REMARKS/ARGUMENTS

Claims 124, 129-131 and 135-145 are pending in this application. Applicants thank the Examiner for withdrawing the continuity objection and written description objections. The rejections to the presently pending claims are respectfully traversed.

Claim Rejections – 35 U.S.C. §101 and §112, First Paragraph

Claims 124, 129-131 and 135-145 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility." (Page 3 of the instant Office Action). Claims 124, 129-131 and 135-145 are further rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention." (Page 12 of the instant Office Action). Applicants respectfully disagree with and traverse these rejections.

The Examiner maintains that the present specification fails to disclose the physiological significance of the PRO1153 gene, or the significance of the genes in lung adenocarcinomas and squamous cell carcinomas. (Page 4, lines 3-7). The Examiner continues to reject the instant nucleic acid case asserting that "there is no evidence regarding whether or not PRO1153 mRNA or polypeptide levels are also increased in these cancers." (Page 5, lines 8-10). The Examiner alleges that "the specification provides data showing a very small increase in DNA copy number in two different types of tumor tissue…." (Page 5 of the instant Office Action). The Examiner also repeats previously cited Hu *et al.*, to assert "the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue." (Page 7 of the instant Office Action). The Examiner also repeats her rejection based on Pennica *et al.*, which was previously argued and these arguments are not repeated here for brevity. The Examiner further asserts that "because the proper control was not used, it is not known if the gene is amplified compared to normal *matched* tissues." (Page 8 of the instant Office Action).

Applicants respectfully traverse this rejection for the reasons outlined below.

Arguments

As a preliminary matter, Applicants respectfully submit that this is a nucleic acid case, therefore any rejection or reference to polypeptides are not argued further in the instant response.

Applicants further submit that all normal tissues have the same gene copy numbers. Accordingly, there is no requirement to match tissues or sample subjects in an assay designed to measure gene amplification. Applicants further submit that the negative control *i.e.,* the "pooled normal blood controls" taught in the specification was known in the art at the time of filing, and accepted as a true negative control as demonstrated by use in peer reviewed publications. For example, in Pitti *et al.* (Exhibit F of Dr. Audrey Goddard's Declaration submitted with the Supplemental Response to Final Office Action filed on August 25, 2005), the authors used the same quantitative TaqMan PCR assay described in the specification to study gene amplification in lung and squamous cancer of DcR3, a decoy receptor for Fas ligand. As described, Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and squamous tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1; Emphasis added). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.* (Exhibit G of Dr. Audrey Goddard's Declaration submitted with the Supplemental Response to Final Office Action filed on August 25, 2005), the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, ccnd1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients. (Page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2), thus confirming the validity of the negative control. Accordingly, the art demonstrates that pooled normal blood samples are considered to be a valid negative control for gene amplification experiments of the type described in the specification.

Applicants have also respectfully pointed out that the observed increase in PRO1153 gene amplification in lung and squamous tumors is not "small" but **significant**, as has been discussed in detail in the previous responses and the Appeal Brief filed on November 14, 2005. Applicants

have repeatedly argued that gene amplification, an essential mechanism for oncogene activation, is well-described in Example 170, page 539 of the present application. Gene amplification was monitored using real-time quantitative TaqMan™ PCR and the results are set forth in Table 9B. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on." (Emphasis added). Applicants show that PRO1153 showed approximately 1.11-1.51 ΔCt units which corresponds to $2^{1.11}$-$2^{1.51}$- fold amplification or **2.16 to 2.85-fold** amplification in lung tumors, which is significant and thus the PRO1153 gene has utility as a diagnostic marker of human lung and squamous cancer.

The Examiner further repeats the rejection based on Sen *et al.*, asserting that the data were not corrected for aneuploidy. (Page 5 of the instant Office Action).

Sen *et al.*

Sen *et al.* indicates that aneuploidy can be a feature of damaged, pre-cancerous tissue and cancerous tissue. Sen *et al.* in fact support the Applicants' position that PRO1153 is still useful in diagnosing at least pre-cancerous lesions or cancer itself. Many articles published around November 19, 2001 (the filing date of this application) studied such damaged or premalignant lesions and suggested that identification of such pre-cancerous lesions were very important in preventive diagnosis and treatment of colon cancer. Based on the well-known art, Applicants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk.

Taken together, even if the observed PRO1153 gene amplification were due to chromosomal aneuploidy (which Applicants do not concede), such an observation would actually support utility for the PRO1153 gene. Whether PRO1153's gene amplification is due to aneuploidy or not, it helps identify pre-cancerous or cancerous lung or squamous lesions and thus, helps in identifying individuals at significantly increased cancer risk. One skilled in the art would clearly have known the value of early detection for cancer, and would have welcomed information in advance about cancer risk, which would help in the prognosis and therapy for lung or squamous cancer. Accordingly, the instant nucleic acids find utility as a diagnostic for lung or

squamous cancer, or at least for identifying individuals at risk for developing lung or squamous cancer.

In conclusion, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO1153 gene, for example, in detecting over-expression or absence of expression of PRO1153. Based on these discussions, one skilled in the art, at the time the application was filed, would know how to use the claimed nucleic acids. Hence, these data clearly support a role for PRO1153 and the claimed gene products, as a lung or squamous tumor markers.

Accordingly, the present 35 U.S.C. §101 and §112, first paragraph, utility rejections should be withdrawn.

CONCLUSION

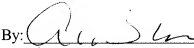
The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-2730 P1C63**).

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: January 31, 2007

By: 
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